

2017 (v3.0) Proposed changes to v2.1 of the Criteria for the clinical use of intravenous immunoglobulin in Australia

<p>v2.1 CONDITION NAME: Solid organ transplantation (other than kidney)</p> <p>PREVIOUS PUBLIC CONSULTATION NAME: Solid organ transplantation (other than kidney)</p> <p>v3.0 CONDITION NAME: Solid organ transplantation (other than kidney)</p>	
<p>Solid organ transplantation (other than kidney) has already been endorsed by NIGAC and JBC with criteria as a condition for which Ig has an emerging therapeutic role. At the time, the need for further review was acknowledged by the Specialist Working Group and this review has now been completed as part of the current Specialist Working Group work program.</p> <p>PROPOSED APPROACH:</p> <p>To retain Solid organ transplantation (other than kidney) in <i>Emerging therapeutic role</i> with the changes as outlined.</p>	<p>SUMMARY OF RATIONALE:</p> <p>The recommended changes are supported by factors including that:</p> <ul style="list-style-type: none"> - Access to ongoing (rather than one-off) Ig treatment is required for desensitisation of patients awaiting heart, and occasionally, lung or other organ transplants because the availability of organ donors is sporadic and patients must already be in an optimised state to be selected to receive an organ, which is lifesaving. - This established practice is being accommodated currently within v2.1 via work-around solutions. The indication would be better managed by the development of formal criteria and access to maintenance therapy for a maximum of six months which is deemed sufficient. As in kidney transplantation, a clinical response will need to be demonstrated after two months Ig therapy for authorisation of the final four months' treatment. - Ig use in Solid organ transplantation (other than kidney) has been steadily increasing in line with the investment made by governments in these programs over the last few years and this trend is expected to continue. There is not expected to be any impact on demand due to the proposed changes as they reflect current clinical practice. - Treatment for 'de-sensitisation of patients who are highly sensitised and unlikely to otherwise receive a transplant' is included in the Canadian (Ontario Regional Blood Coordinating Network, 2016) guidelines. The UK guidelines (UK Department of Health, 2011) include desensitisation of antibody incompatible solid organ transplantation as a 'blue' or medium priority in times of shortage but recommended for use.
<p>v2.1 CONDITION CATEGORY: Condition for which Ig has an emerging therapeutic role (Chapter 6)</p> <p>2015 PUBLIC CONSULTATION CATEGORY: Condition for which Ig has an emerging therapeutic role (Chapter 6)</p> <p>v3.0 CONDITION CATEGORY: Condition for which Ig has an emerging therapeutic role (Chapter 6)</p>	

Role of Ig therapy: Ig therapy plays an important immunomodulatory role in incompatible organ transplantation with proven benefit (Level 1 evidence) for desensitisation of highly sensitised patients pre-transplant to improve transplant rates and clinical outcomes (Jordan, 2004). In heart transplant, the approach to desensitise is reasonably common because of the increasing use of device technology (and exposure to blood transfusion), so there is an increasing population of sensitised patients that would not be considered for transplant without desensitisation. Desensitisation is only an occasional occurrence in lung transplantation.

In antibody mediated rejection, the underlying mechanisms of therapy include suppression of the T-cell response (steroids, mycophenolate mofetil, anti-lymphocyte antibodies), elimination of circulating antibodies (plasmapheresis), inhibition of residual antibodies (IVIg therapy), suppression or depletion of B cells (steroids, rituximab, splenectomy), inhibition of complement (eculizumab, IVIg therapy) (Colvin, 2015).

There are a number of potential mechanisms of action reported for Ig therapy in this context. These include inhibition of complement activation by the Fc fragment of IgG molecules in the IVIg preparations, or possible contamination of IVIg products with soluble HLA molecules (Wanatabe, 2005).

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Condition Name	Solid organ transplantation (other than kidney)	Solid organ transplantation (other than kidney)	Unchanged
Specialty	Transplantation	Transplantation	Unchanged
Category	<i>Emerging therapeutic role</i>	<i>Emerging therapeutic role</i>	Unchanged
Specific Conditions	<ul style="list-style-type: none"> • Heart • Lung • Heart & Lung • Liver • Heart kidney • Heart liver • Liver kidney • Pancreas • Small intestine 	<ul style="list-style-type: none"> • Heart • Lung • Heart & Lung • Liver • Heart kidney • Heart liver • Liver kidney • Pancreas • Small intestine 	Unchanged
Level of	Small case studies only; insufficient data	Insufficient data (Category 4a)	Unchanged

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Evidence	(Category 4a)		
Justification for Evidence Category	<p>Jordan et al (1998) combined data from seven renal transplant recipients and three heart transplant recipients with steroid-resistant combined antibody-mediated (AbMR) and cellular rejection. All patients in this series were successfully treated with high-dose IVIg.</p> <p>Findings from an International Consensus Conference in 2011 noted that IVIg has never been systematically studied in patients after transplant to prophylactically reduce the incidence of AbMR. Despite being routinely used for the treatment of AbMR, only 1 study has reported the efficacy of Ig therapy in this setting. Five patients with evidence of AbMR were treated with a combination of IVIg and plasmapheresis. Hemodynamics initially improved in all 5 patients, but 2 patients later required further therapy with rituximab because of recurrent hemodynamic rejection.</p>	<p>Ig therapy plays an important immunomodulatory role in incompatible organ transplantation with proven benefit (Level 1 evidence) for desensitisation of highly sensitised patients pre-transplant to improve transplant rates and clinical outcomes (Jordan, 2004). For desensitisation, trials have demonstrated improved outcomes when IVIg is used in association with Rituximab and/or other immunosuppressant agents.</p> <p>Jordan et al (1998) combined data from seven renal transplant recipients and three heart transplant recipients with steroid-resistant combined antibody-mediated (AbMR) and cellular rejection. All patients in this series were successfully treated with high-dose IVIg.</p> <p>Findings from an International Consensus Conference in 2011 noted that IVIg has never been systematically studied in patients after transplant to prophylactically reduce the incidence of AbMR. Despite being routinely used for the treatment of AbMR, only 1 study has reported the efficacy of Ig therapy in this setting. Five patients with evidence of AbMR were treated with a combination of IVIg and plasmapheresis. Hemodynamics initially improved in all 5 patients, but 2 patients later required further therapy with rituximab because of</p>	<p>This section has been strengthened to include supporting evidence for desensitisation and additional literature related to antibody mediated rejection.</p>

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		<p>recurrent hemodynamic rejection. The role of Ig therapy in antibody mediated rejection is confirmed in a recent Scientific Statement of the American Heart Association (Colvin, 2015).</p>	
Indications	<p>Pre - transplant where donor specific antibody/antibodies prevent transplantation (HLA or anti-blood group) in highly sensitised patients</p> <p>Post-transplant - acute anti-body mediated rejection with clinical evidence of graft dysfunction</p> <p>Treatment or prevention of graft rejection where conventional immunosuppressive therapies is contraindicated or pose a threat to the graft or patient</p>	<p>De-sensitisation of patients to improve the likelihood of transplantation</p> <p>Post-transplant - acute anti-body mediated rejection</p> <p>Treatment or prevention of graft rejection where conventional immunosuppressive therapies is contraindicated or pose a threat to the graft or patient</p>	<p>The first indication has been amended since 2015 to better describe clinical practice including maintaining consistency with Kidney transplantation for access to Ig treatment for up to six months. One-off treatment is not required for these patients as there is no planned desensitisation for a living donor organ.</p> <p>The second indication has been amended to more accurately reflect the fact that clinical evidence of graft dysfunction is not always required - a one-off request may be approved in the early period of rejection where there is a high clinical suspicion. The criteria themselves have not changed and this change is consistent with Kidney transplantation.</p>
Description and Diagnostic Criteria	<p>Transplant rejection occurs when a recipient's immune system attacks a transplanted organ or tissue. Despite the use of immunosuppressants, one or more episodes of rejection can occur after transplantation. Both cellular and humoral (antibody-mediated) effector mechanisms can play a role. The presence and pattern of rejection</p>	<p>In heart transplant, the approach to desensitise patients is reasonably common because of the increasing use of device technology (and exposure to blood transfusion), so there is an increasing population of sensitised patients that would not be considered for transplant without this approach.</p> <p>Desensitisation is only an occasional occurrence in lung transplantation.</p>	<p>A short description relating to desensitisation has been added.</p>

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	<p>need to be established by biopsy. Laboratory tests to assess the presence and strength of antibodies to the donor antigens can provide additional useful information. Clinical assessment, blood tests, ultrasound and nuclear imaging are used primarily to exclude other causes of organ dysfunction. Acute cellular rejection occurs in 15–30% of organ transplants and is responsive to steroids in more than 90% of cases. When rejection is steroid resistant, IVIg is a safer therapy than anti-T cell antibody therapy with equal efficacy. Antibody mediated rejection (AbMR) occurs in 10–20% of heart transplants that have been performed with a compatible cross match. AbMR is associated with increased incidence of graft dysfunction, coronary allograft vasculopathy and mortality. Before the use of IVIg and plasma exchange, AbMR failed to respond adequately to therapy in most cases. Additionally, complications from therapy were severe and sometimes fatal. AbMR responds to IVIg with or without plasma exchange in more than 85% of patients. Diagnostic criteria for AbMR must be</p>	<p>Transplant rejection occurs when a recipient’s immune system attacks a transplanted organ or tissue. Despite the use of immunosuppressants, one or more episodes of rejection can occur after transplantation. Both cellular and humoral (antibody-mediated) effector mechanisms can play a role. The presence and pattern of rejection need to be established by biopsy. Laboratory tests to assess the presence and strength of antibodies to the donor antigens can provide additional useful information. Clinical assessment, blood tests, ultrasound and nuclear imaging are used primarily to exclude other causes of organ dysfunction. Acute cellular rejection occurs in 15–30% of organ transplants and is responsive to steroids in more than 90% of cases. When rejection is steroid resistant, IVIg is a safer therapy than anti-T cell antibody therapy with equal efficacy. Antibody mediated rejection (AbMR) occurs in 10–20% of heart transplants that have been performed with a compatible cross match. AbMR is associated with increased incidence of graft dysfunction, coronary allograft vasculopathy and mortality. Before the use of IVIg and plasma exchange, AbMR failed to respond adequately to therapy in most cases. Additionally, complications from therapy were severe and sometimes fatal. AbMR responds to IVIg with or without plasma exchange in more than 85% of patients. Diagnostic criteria for AbMR must be consistent</p>	

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	consistent with the International Society for Heart and Lung Transplantation (IHSLT) Criteria (2011).	with the International Society for Heart and Lung Transplantation (IHSLT) Criteria (2011).			
Diagnosis is required		No	By which specialty		Unchanged
Diagnosis must be verified		No	By which specialty		
Exclusion Criteria					
Qualifying Criteria	<p>Pre - transplant where donor specific antibody/antibodies prevent transplantation (HLA and/or anti-blood group)</p> <ul style="list-style-type: none"> • ABO incompatible transplant planned with or without HLA antibody or antibodies (minimum of 500 MFI) preventing organ transplantation. 	<p>De-sensitisation of patients to increase the likelihood of transplantation</p> <ul style="list-style-type: none"> • Highly sensitised patient with known antibody(ies) of at least 1000 MFI <p>AND</p> <ul style="list-style-type: none"> • Circumstances indicate that the likelihood of receiving an organ is very low 			<p>The first indication has been revised to be consistent with the changes to kidney transplantation and now require a higher barrier to entry for the level of antibody for access to ongoing therapy.</p>

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	<p>Post-transplant - active acute antibody mediated rejection</p> <ul style="list-style-type: none"> • Presence of incompatible ABO blood group donor specific antibody/antibodies and/or donor specific HLA antibody / antibodies (at least a minimum of 500 MFI) <p>AND</p> <ul style="list-style-type: none"> • Current clinical and laboratory evidence of graft dysfunction where biopsy not available <p>OR</p> <ul style="list-style-type: none"> • Organ biopsy demonstrates antibody mediated rejection according to Banff or IHSLT criteria¹ <p>OR</p> <ul style="list-style-type: none"> • There is a high clinical suspicion that it is antibody mediated rejection and evidence not yet available (one-off request in early period of acute rejection). 	<p>Post-transplant - active acute antibody mediated rejection</p> <ul style="list-style-type: none"> • Presence of incompatible ABO blood group donor specific antibody/antibodies and/or donor specific HLA antibody / antibodies (at least a minimum of 500 MFI) <p>AND</p> <ul style="list-style-type: none"> • Current clinical and laboratory evidence of graft dysfunction where biopsy not available <p>OR</p> <ul style="list-style-type: none"> • Organ biopsy demonstrates antibody mediated rejection according to Banff or IHSLT criteria (Berry et al, 2005-2011) <p>OR</p> <ul style="list-style-type: none"> • There is a high clinical suspicion that it is antibody mediated rejection and evidence not yet available (one-off request in early period of acute rejection). 	<p>Criteria for the second two indications are unchanged from 2015.</p>

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	<p>For a 2nd dose, Donor Specific Antibody(ies) must be proven and biopsy must be abnormal but may not yet be diagnostic meeting all of the IHSLT1 criteria. For subsequent doses, all IHSLT criteria on biopsy must be met.</p> <p><i>1 The ISHLT working formulation for pathologic diagnosis of antibody-mediated rejection in heart transplantation: Evolution and current status (2005–2011) Berry et al JHLT 2011.</i></p> <p>Treatment or prevention of graft rejection where conventional immunosuppressive therapies is contraindicated or pose a threat to the graft or patient</p> <ul style="list-style-type: none"> • Conventional immunosuppressive therapy is 	<p>For second dose, Donor Specific Antibody(ies) must be proven and biopsy must be abnormal but may not yet be meeting all of the IHSLT (Berry et al, 2005-2011) diagnostic criteria. For subsequent doses, all IHSLT criteria on biopsy must be met.</p> <p>Treatment or prevention of graft rejection where conventional immunosuppressive therapies is contraindicated or pose a threat to the graft or patient</p> <ul style="list-style-type: none"> • Conventional immunosuppressive therapy is contraindicated and the reason is provided. 	

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	<p>contraindicated and the reason is provided.</p>		
<p>Review Criteria</p>	<p>No review is required for one-off dosing</p>	<p>De-sensitisation of patients to improve the likelihood of transplantation</p> <p>Review by a Transplantation Specialist is required within 2 months of treatment to determine whether the patient has responded. If no response, Ig therapy should be ceased. The maximum period of treatment is six months.</p> <p>Documentation of clinical effectiveness is necessary for continuation of Ig therapy.</p> <p>On review of the initial authorisation period</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> • Reduction in the level of HLA Antibody(ies) as demonstrated by a decrease in the MFI (or functional reactivity) compared to the qualifying assessment <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • A reduction in non-HLA Ab, if relevant <p>AND</p>	<p>After an initial authorisation period of two months, patients must demonstrate a clinical response to Ig therapy by either a reduction in antibody level or a measurable reduction in functional antibody reactivity. If this is demonstrated, a further four months Ig therapy may be authorised.</p> <p>A total of six months treatment is available.</p>

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		<ul style="list-style-type: none"> • Specific circumstances exist to justify treatment for a further course <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • The patient has received an organ <p>Post-transplant - acute anti-body mediated rejection</p> <p>Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy.</p> <p>Clinical effectiveness of Ig therapy may be demonstrated by:</p> <ul style="list-style-type: none"> • Reduction in antibody level • Reduction in evidence of graft rejection on biopsy • Improvement in graft function <p>Treatment or prevention of graft rejection where conventional immunosuppressive therapies is contraindicated or pose a threat to the graft or patient</p> <p>Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy.</p> <p>Clinical effectiveness of Ig therapy may be</p>	<p>Outcome measures have been developed for the second two indications.</p>

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		demonstrated by: <ul style="list-style-type: none"> • Reduction in evidence of rejection on biopsy • Improvement in graft function 	
Dose	<p>IVIg with plasma exchange 0.1 to 0.5 g/kg after each exchange (Total maximum dose of 2.5g/Kg divided over 5 doses).</p> <p>IVIg without plasma exchange (single dose) Up to 2 g/kg to a maximum of 140 g as a single dose</p> <p>IVIg without plasma exchange (divided dose) 2 to 3.5g/kg in a divided dose</p> <p>Dosing above 1 g/kg per day is contraindicated for some IVIg products.</p> <p>Refer to the current product information sheet for further information.</p> <p>The aim should be to use the lowest dose possible that achieves the</p>	<p>De-sensitisation of patients to increase the likelihood of transplantation</p> <p>IVIg with plasma exchange: 0.1 to 0.5 g/kg after each exchange (Total maximum dose of 2.0g/Kg across divided doses monthly)</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient</p> <p>Refer to the current product information sheet for further information on dose, administration and contraindications.</p> <p>Post-transplant - acute anti-body mediated rejection</p> <p>IVIg with plasma exchange 0.1 to 0.5 g/kg after each exchange (Total maximum dose of 2.5g/Kg divided over 5 doses).</p> <p>IVIg without plasma exchange (single dose) Up to 2 g/kg to a maximum of 140 g as a single dose</p>	<p>Dosing has been amended for the revised first indication, now being limited to Ig treatment in association with plasmapheresis only.</p> <p>Dosing controls for the second two indications are unchanged from 2015.</p>

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	<p>appropriate clinical outcome for each patient.</p>	<p>IVIg without plasma exchange (divided dose) 2 to 3.5g/kg in a divided dose</p> <p>Refer to the current product information sheet for further information on dose, administration and contraindications.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> <p>Treatment or prevention of graft rejection where conventional immunosuppressive therapies is contraindicated or pose a threat to the graft or patient</p> <p>Dose Type: IVIg with plasma exchange 0.1 to 0.5 g/kg after each exchange (Total maximum dose of 2.5g/Kg divided over 5 doses).</p> <p>IVIg without plasma exchange (single dose): Up to 2 g/kg to a maximum of 140 g as a single dose</p> <p>IVIg without plasma exchange (divided dose): 2 to 3.5g/kg in a divided dose</p> <p>Refer to the current product information sheet for further information on dose, administration and</p>	

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		<p>contraindications.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p>	
<p>References (most recent update: February 2016)</p>			
<p>Berry G et al (2005-2011) The ISHLT working formulation for pathologic diagnosis of antibody-mediated rejection in heart transplantation: Evolution and current status. <i>The Journal of Heart and Lung Transplant</i>, 30(6): 601:611.</p> <p>http://www.jhltonline.org/article/S1053-2498(11)00796-0/abstract</p> <p>Colvin MM, Cook JL, et al (2015) Antibody mediated rejection in cardiac Transplantation: Emerging knowledge in Diagnosis and Management. A Scientific statement from the American Heart Association. <i>Circulation</i>, 131:1608-1639.</p> <p>https://www.ncbi.nlm.nih.gov/pubmed/25838326</p> <p>Jordan, SC, Vo, A, Bunnapradist, S, et al (2003) Intravenous immune globulin treatment inhibits cross match positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients. <i>Transplantation</i>, 76(4): 631–6.</p> <p>https://www.ncbi.nlm.nih.gov/pubmed/12973100</p> <p>Ontario Regional Blood Coordinating Network (2016). Ontario Intravenous Immune Globulin (IVIg) Utilization Management Guidelines, Version 3.0. [online]. Available at: http://transfusionontario.org/en/download/ontario-intravenous-immune-globulin-IVIg-utilization-management-guidelines-2/.</p> <p>UK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update. Available at:</p>			

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216671/dh_131107.pdf

UK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update: Summary Poster. Available at: https://www.igd.nhs.uk/wp-content/uploads/2016/04/DemandManagementPoster_v4_February2016.pdf

POTENTIAL OPERATIONAL IMPACT						
There is unlikely to be any significant operational impact due to the proposed changes, apart from a reduced workload for staff re-ordering as access to ongoing treatment will be available for these patients.						
POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE						
Description of impact on patients:		The further changes that have been made to the previously revised criteria define circumstances in which access to ongoing Ig treatment can be requested for patients undergoing solid organ transplantation. The circumstances are aligned with current clinical practice to improve the likelihood for highly sensitised patients to be able to receive an organ. In order to confirm that Ig therapy is achieving the expected clinical benefit, a formal review of the patient's clinical response will be made after two months of treatment and if a response is demonstrated, treatment for a further four months can be authorised. When a response has not been achieved after two months, Ig therapy will cease and patients will require an alternative treatment approach. A maximum treatment period of six months will be provided for patients as this has been determined as sufficient Ig treatment time for a sustained change to be achieved. After this time, alternative treatment approaches should be used, if required.				
Impact on demand:		It is acknowledged that due to governments' investment in organ transplantation over the last few years, the trend of increasing use for this condition is likely to continue. There is not expected to be any impact on Ig use as a result of the proposed changes.				
	2011-12	2012-13	2013-14	2014-15	2015-16	The Specialist Working Group estimated magnitude of effect: No impact against projected demand
Patient number	99	107	104	130	144	
Total Grams issued	12591	17427	14946	22036	24267	
% Total Grams issued	0.38%	0.48%	0.37%	0.49%	0.49%	
Specialist Working Group knowledge development opportunities and recommendations						
None identified at this stage.						

END OF PUBLIC CONSULTATION DOCUMENT

Next review: Twelve to eighteen months from BloodSTAR v3.0 implementation